Solving electrolyte disturbances with the Ehrlich reagent

Adrian Schreiber, Saban Elitok and Ralph Kettritz
HELIOS Klinikum Berlin, Franz Volhard Clinic and First Department of Internal Medicine, Medical Faculty of the Charité, Humboldt University of Berlin, Berlin, Germany

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Case

A 57-year-old female was admitted because of poorly controlled hypertension and dyspnoea when climbing stairs. She had been given a thiazide diuretic, a calcium antagonist and an angiotensin converting enzyme inhibitor. On further questioning she indicated that she had a life-long history of intermittent abdominal discomfort. She had moderate hypertensive eyeground changes. Her electrocardiogram was non-specific; however, an echocardiogram was consistent with moderate cardiac hypertrophy and diastolic dysfunction. Her serum sodium was 127 mmol/l. Her urine appeared normal and her urinalysis was normal with the exception of a highly positive urobilinogen determination on the test-strip [1]. The life-long history of intermittent abdominal pain together with the appearance of high amounts of urobilinogen raised our suspicion for porphyrins. Therefore, we performed a simple test using Ehrlich’s reagent. The appearance of her urine, and that of one of the authors as a control after the addition of Ehrlich’s reagent, is shown in Figure 1 [2].

The patient had two daughters with the same complaints. A son and her husband never had abdominal pain. The patient has acute intermittent porphyria. She also has hypertension and diastolic cardiac dysfunction. Acute intermittent porphyria obviously does not protect from hypertension or cardiovascular disease.

Discussion

The porphyrias are a group of diseases characterized by overproduction of porphyrin compounds and their precursors [3]. In animals, porphyrin synthesis is required to make iron-containing haeme and mitochondrial cytochromes, whereas in plants, the magnesium-containing chlorophyll catalyses photosynthesis. Thus, as their Nobel prize-winning discoverer Hans Fischer stated, ‘porphyrins are the substances that make blood red and grass green’ [4].

Porphyrias are synthesized from glycine and succinyl-CoA by a series of enzymatic steps as shown in Figure 2 [5]. The first step requires delta-aminolevulinic acid synthase (ALAS) to make delta-aminolevulinic acid; the second requires delta-aminolevulinic acid dehydratase to make porphobilinogen. This enzyme when defective results in plumboporphyria. The next step is the conversion of porphobilinogen to preuroorphyrinogen. This step requires the enzyme porphobilinogen deaminase, which when defective, results in acute intermittent porphyria, as in our patient. Pre-uroorphyrinogen is metabolized to uroporphyrin III by the enzyme uroporphyrin III synthase, which when defective, is responsible for erythropoietic porphyria. Uroporphyrin III is metabolized to coproporphyrin III via uroporphyrinogen decarboxylase that is responsible for porphyria cutanea tarda. Coproporphyrin III is oxidized to protoporphyrinogen IX via coproporphyrinogen oxidase that is responsible for hereditary coproporphyria. This product is metabolized further to protoporphyrin IX via protoporphyrin oxidase, responsible for variegate porphyria. Ferrochelatase is required for the iron insertion to make haeme. A defective ferrochelatase results in protoporphyrin IX. Finally, protoporphyrinogen may form uroporphyrin I that is converted to coproporphyrinogen I by the enzyme uroporphyrinogen decarboxylase. A defect here results in porphyria cutanea tarda.

With the exception of plumboporphyria, the porphyrias are inherited in an autosomal-dominant fashion. The patients are usually heterozygous and are endowed with half-normal enzyme function. Obviously, offspring from two heterozygous parents have a much more severe form of the disease. Because of their symptoms, their inheritance pattern, and visible urinary markers, the porphyrias were recognized early...
as inherited metabolic diseases. A metabolic and molecular genetic understanding of the porphyrias has contributed the clinical evaluation and treatment. Haeme represses the hepatic rate-limiting enzyme delta-aminolevulinic acid synthase or ALAS, thereby reducing hepatic overproduction of porphyrin precursors in the liver, with subsequent relief of symptoms in the acute porphyrias.

The hepatic porphyrias, acute intermittent porphyria, variegate porphyria, hereditary coproporphyria and plumboporphyria, are characterized by neurovisceral attacks. The clinical features are best memorized by the five ‘Ps’: (i) (after) puberty, (ii) pain, (iii) psychiatric disturbances, (iv) polyneuropathy and (v) photosensitivity (only in hereditary coproporphyria and variegate porphyria). The discordance between a fixed inherited defect and a relapsing clinical pattern is explained by delta-aminolevulinic acid synthase ALAS induction. This rate-limiting enzyme can be induced by various factors such as: (i) menses, (ii) medicines (drugs), malnutrition (fasting) and medical (or surgical) illnesses, leading us to the four ‘Ms’. A partial deficiency of a non-rate-limiting enzyme results in a back-up (Ger. Stau) of the metabolic products, causing the clinical manifestations.

Acute intermittent porphyria is fairly common [6]. More than 100 mutations in the gene for porphobilinogen deaminase have been described. The prevalence in Scandinavia has been reported to be 1 in 500, in France 1 in 1500. Family studies have shown that 90% of cases are latent. Furthermore, the expected attacks far exceed those that actually occur, suggesting that many mutations are only mildly expressed. Induction of ALAS leads to accumulation of the precursors.

Fig. 2. Step 1, ALAS, is the rate-limiting enzyme and is inducible. Step 2 is responsible for plumboporphyria. Step 3 is responsible for acute intermittent porphyria. Step 4 causes congenital erythropoietic porphyria. Step 5 causes porphyria cutanea tarda. Step 6 causes hereditary coproporphyria. Step 7 causes variegate porphyria. Step 8 causes protoporphyria. Step 9 can also cause porphyria cutanea tarda.
delta-aminolevulinic acid and porphobilinogen, which are excreted in the urine. Porphobilinogen on standing might spontaneously condense forming porphobilin. Thus, during acute attacks this brownish-red polymer is often visible. Our patient had no acute attack and so we helped matters along a bit by adding the Ehrlich chromogen reagent, the so-called Watson–Schwartz test.

Acute intermittent porphyria varies greatly in its clinical features. Hypothalamic dysfunction may result in the syndrome of inappropriate antidiuretic hormone with hyponatraemia. Our patient was indeed a bit hyponatraemic. However, her thiazide diuretic may have also been contributory here. Our patient had only slight peripheral neuropathy and she was well aware of her illness, as were her children. Thus, she was able to teach us about acute intermittent porphyria. Acute intermittent porphyria should be included in the differential diagnosis of unexplained abdominal pain, acute psychiatric disturbances and acute polyneuropathies. Positive family histories, symptoms that occur during menstruation, or after exposure to new medicines, are helpful clues. A high carbohydrate isocaloric diet is desirable. The use of haematin, the ferric hydroxylated form of heme, for patients whose attacks do not improve rapidly is also an important component of the therapy [7]. Delta-aminolevulinic acid synthase can be suppressed quickly and the enzyme has a short half-life. Thus, plasma and urinary delta-aminolevulinic acid and porphobilinogen concentrations can be reduced rapidly by haematin treatment.

It is important to keep in mind the drugs that can elicit acute attacks (‘unsafe’ drugs). Lengthy tables can be found in major textbooks and reviews. For our patient’s hypertension, we were faced with the fact that a number of drug-favourites of nephrologists are on the list of ‘unsafe’ drugs. These drugs include captopril, diltiazem, furosemide, hydrochlorothiazide, nifedipine and verapamil. Fortunately, none of these drugs has been definitely associated with acute attacks, as have for instance barbiturates, chlordiazepoxide, diazepam and methyl-dopa. Furosemide and hydrochlorothia-

zide are listed with ‘conflicting results’. The other drugs are suspects but have not as yet been proved guilty. Further information is available at the American Porphyria Foundation website (http://www.enterprise.net/apf).

Teaching point

Acute intermittent porphyria is an autosomal-dominant disease characterized by neurovisceral attacks. For nephrologists, the condition is important in that it may induce hyponatraemia, is a ‘urine’ diagnosis, and can be exacerbated by a host of drugs commonly used in nephrology, including antihypertensive agents and diuretics. Paul Ehrlich contributed the chromogen reagent that was long used to make the diagnosis. The method has given way to more reliable techniques; however, the dramatic colour reaction is ever so much more fun!

References

1. Kleeberg J. [Ehrlich’s benzaldehyde reaction (with urobilinogen) 80 years later]. Z Gastroenterol 1982; 20: 424–428